Future of LDL Therapy

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Disclosure

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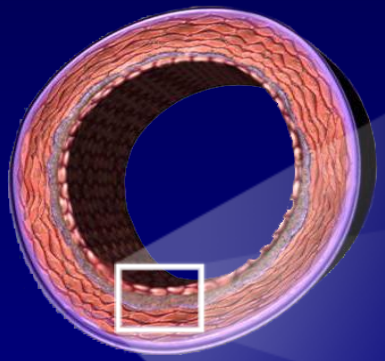
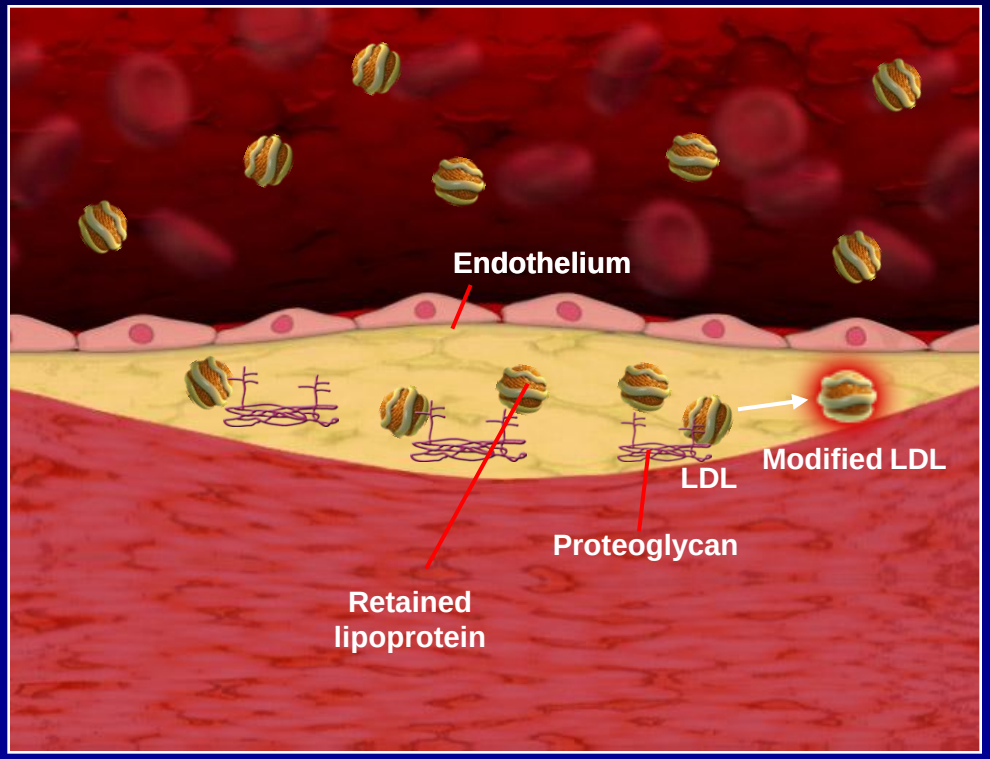
Employment:	**Vanderbilt University**
Research Support:	**NIH-NHLBI**
Clinical Research:	**ISIS/Genzyme**
Advisory:	**Merck, Takeda, Pfizer, Astra-Zeneca**

Response-to-Retention Model of Atherosclerosis

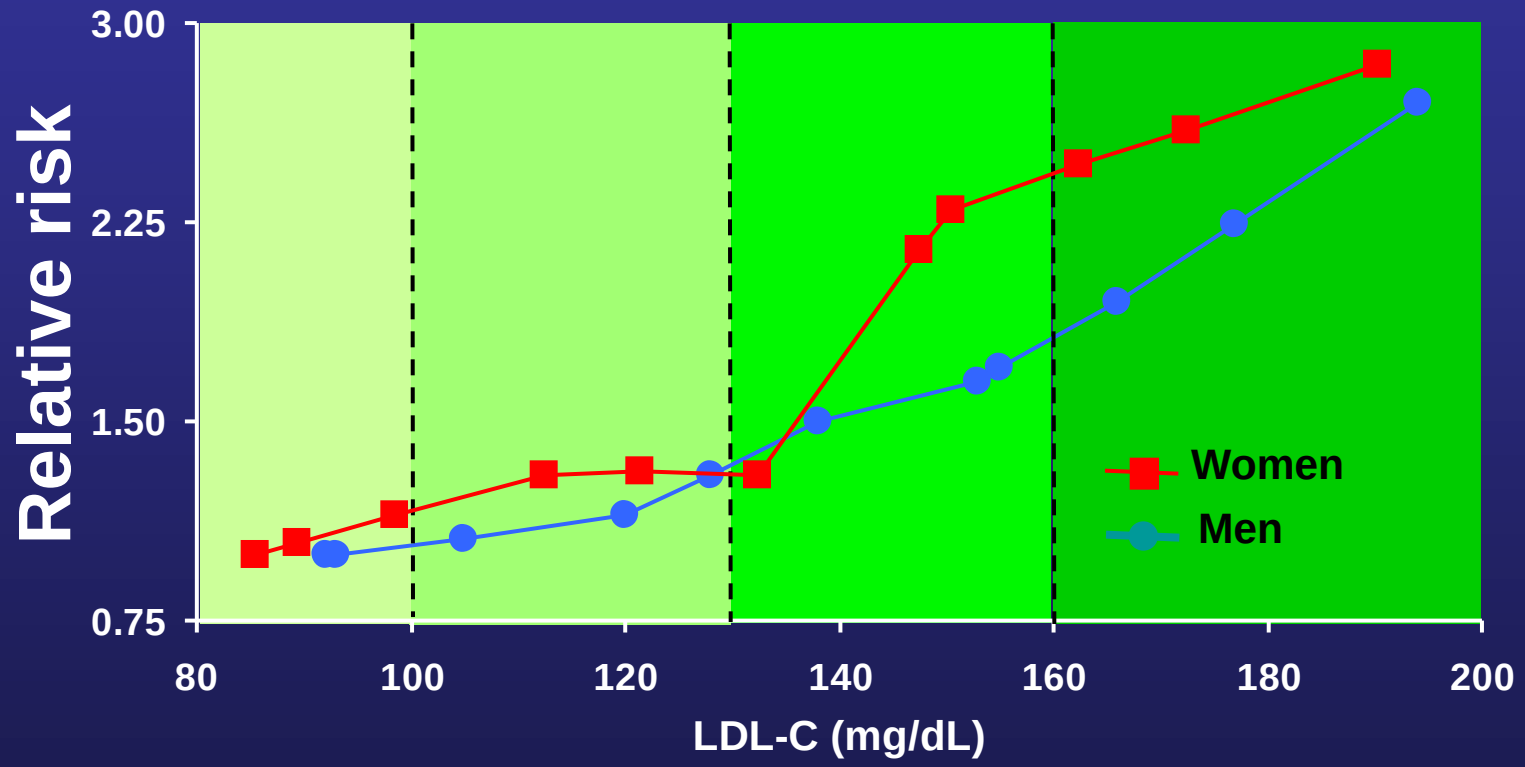


- Lipoproteins are retained by the subendothelial matrix
- Retention leads to LDL oxidation and activation of the inflammatory response



1. Tabas I et al. *Circulation.* 2007;116:1832–1844. 2. Khalil MF et al. *Arterioscler Thromb Vasc Biol*. 2004;24:2211–2218. 3. Jialal I et al. *Circulation*. 2003;107:926–928.

Association Between LDL-C and CHD Risk

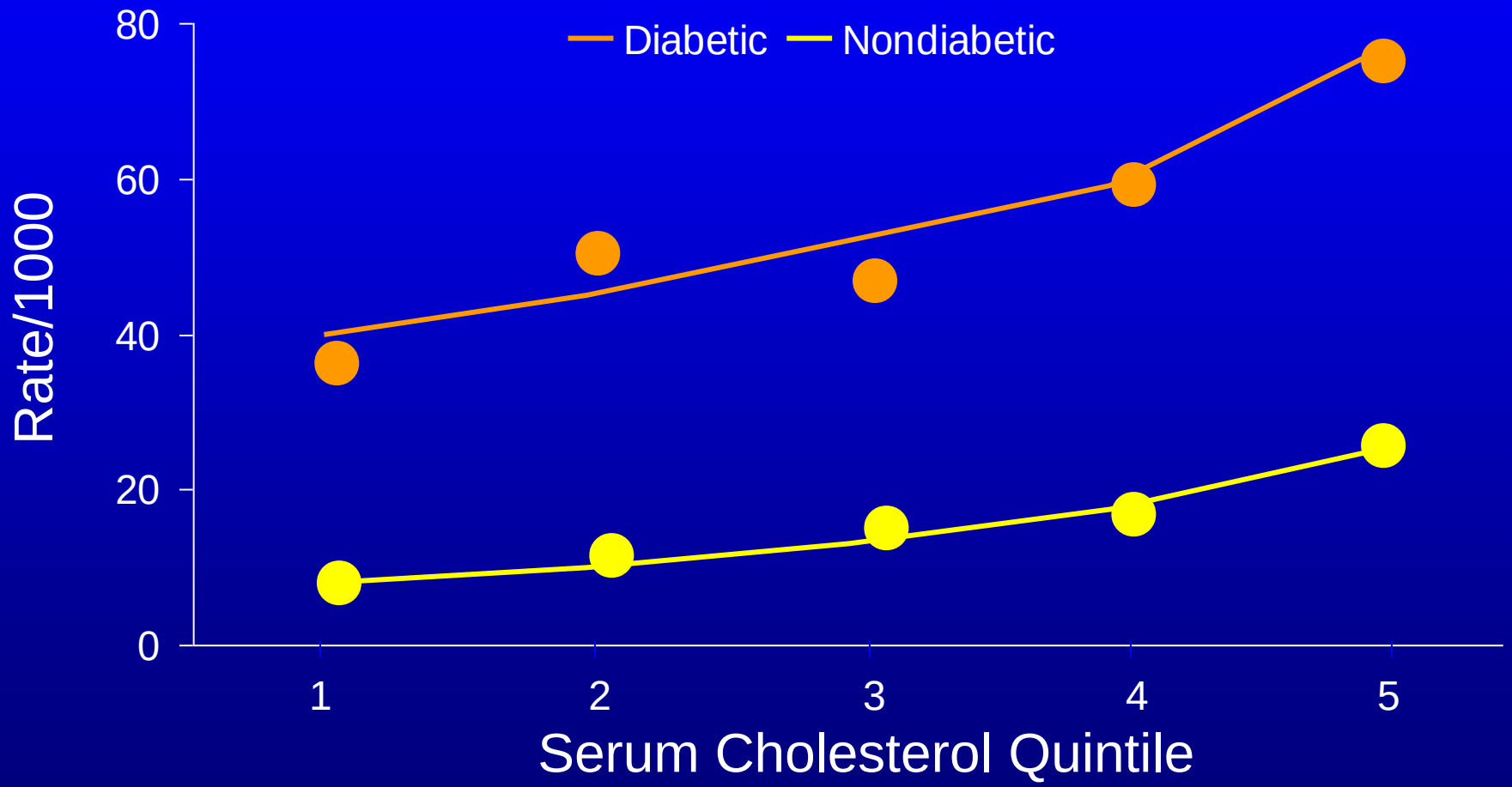


LDL-C = low-density lipoprotein cholesterol.

Adapted from Sharrett et al. *Circulation*. 2001;104:1108-1113.

Total Cholesterol Predicts CHD Mortality in Diabetic and Nondiabetic Men

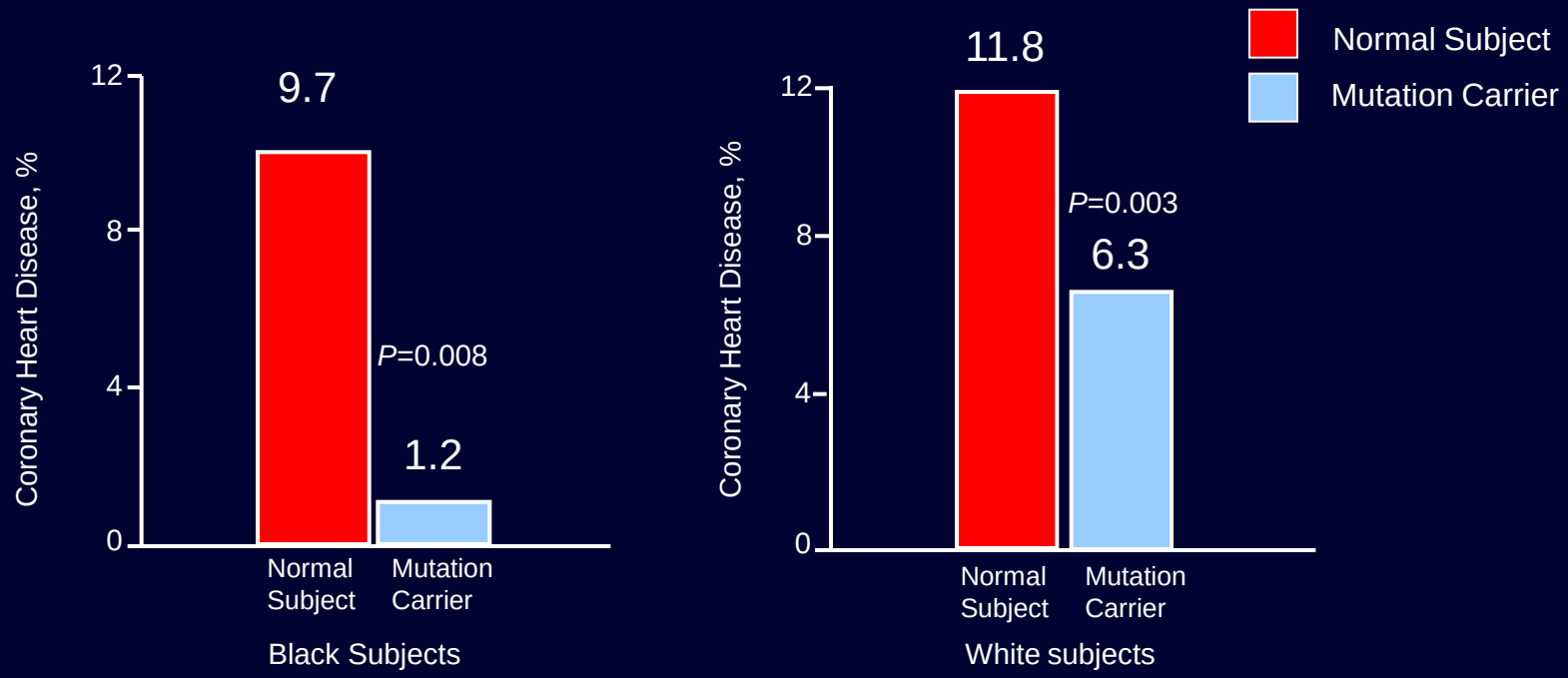
Multiple Risk Factor Intervention Trial (MRFIT)



Bierman EL, *Arteriosder Thromb*, June 1992
Based on data from J. Stamler

Reduced CHD Incidence in Individuals With Low LDL-C Levels Due to PCSK9 Mutations

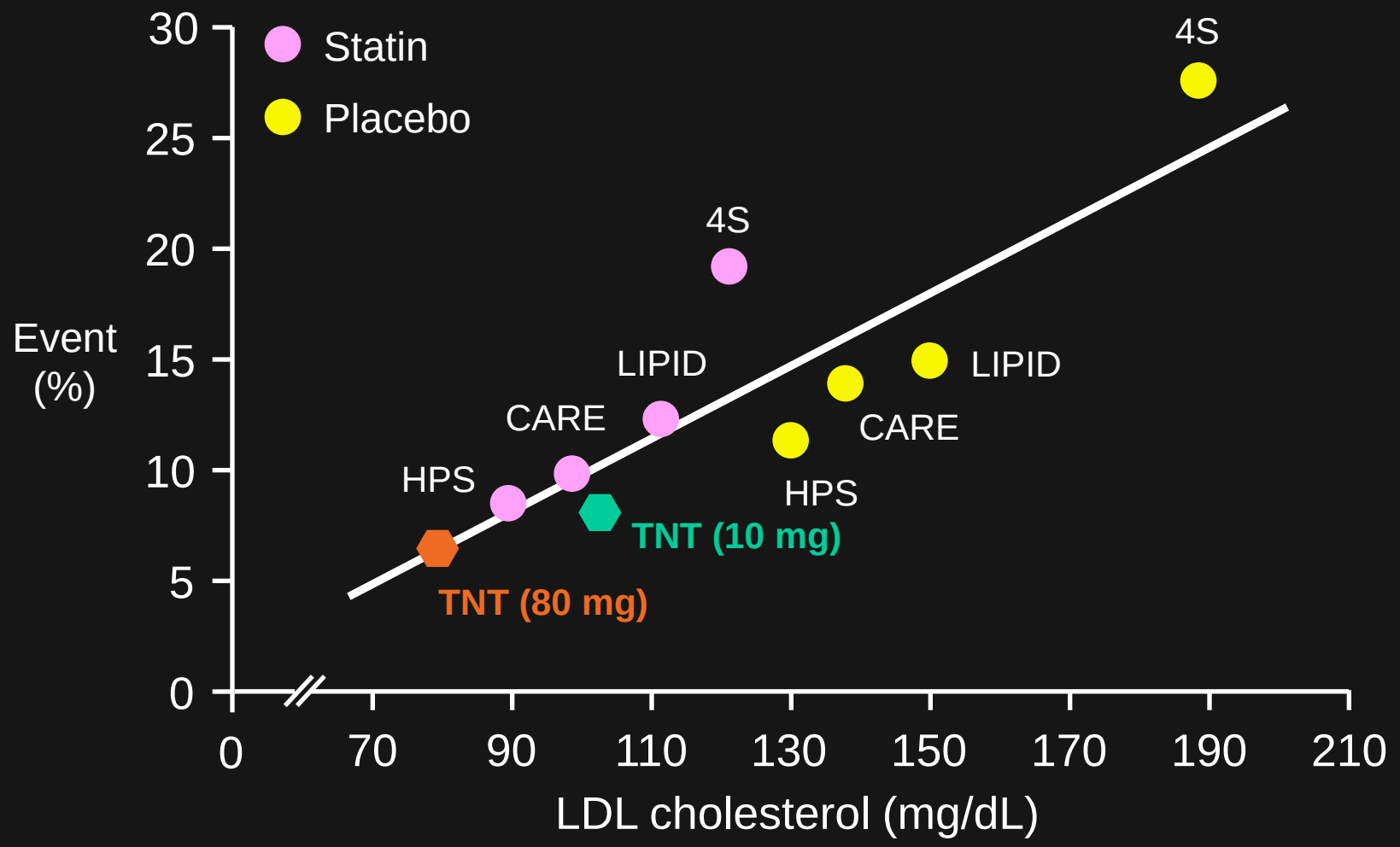
- PCSK9 plays a role in cholesterol homeostasis by regulating LDLR expression
- PCSK9 loss-of-function mutations cause low cholesterol (20% to 40% less than normal)



PCSK9 = proprotein convertase subtilisin/kexin type 9 serine protease.

1. Rashid S et al. *PNAS*. 2005;102(15):5374–5379. 2. Cohen JC et al. *Nat Genet*. 2005;37(2):161–165. 3. Kotowski IK et al. *Am J Hum Genet*. 2006;78(3):410–422. 4. Cohen JC et al. *N Engl J Med*. 2006;354(12):1264–1272.

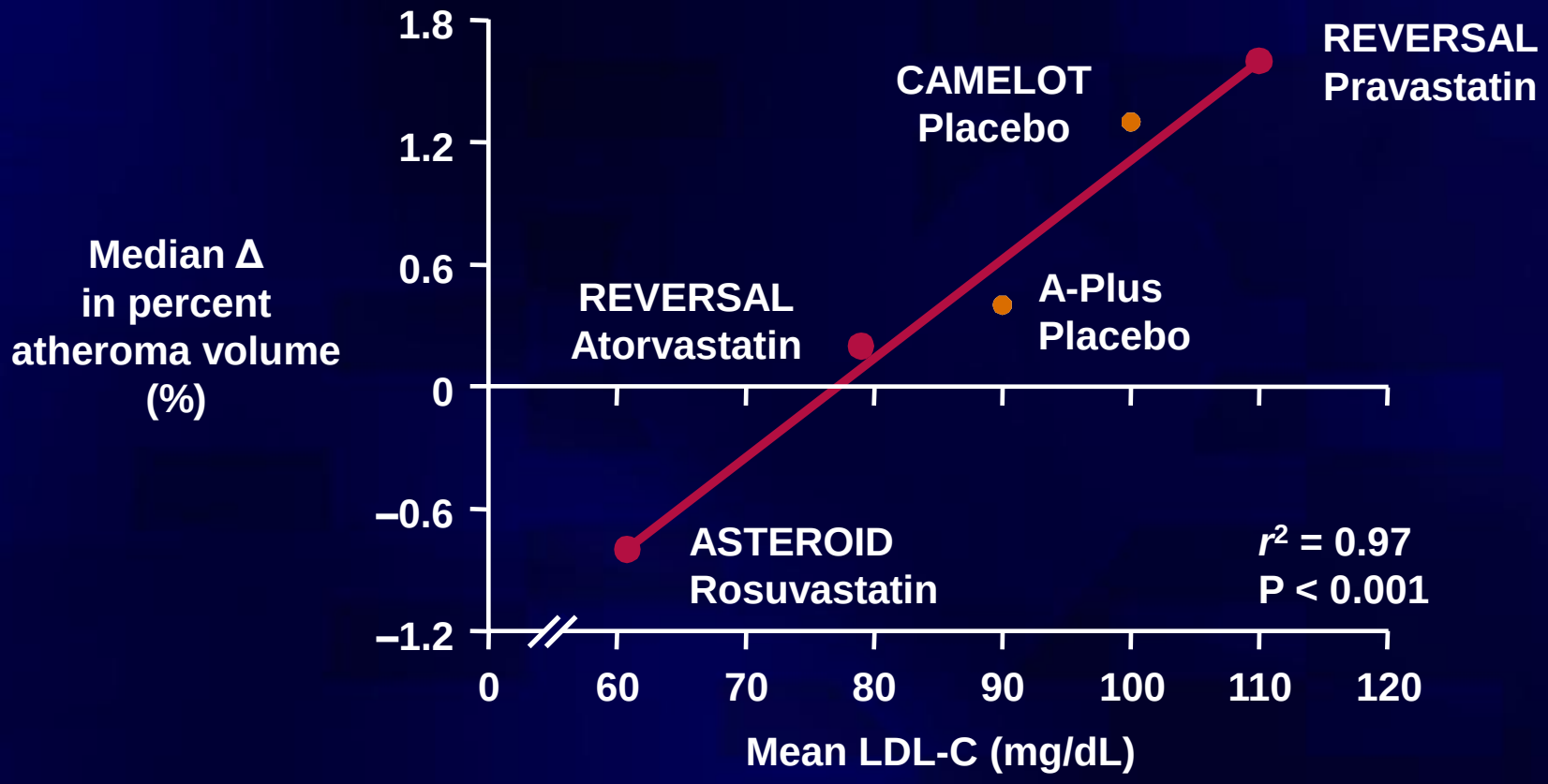
Benefits of Intensive LDL-C Lowering



LaRosa JC et al. *N Engl J Med.* 2005;352.

Relationship between ↓LDL-C and atheroma burden

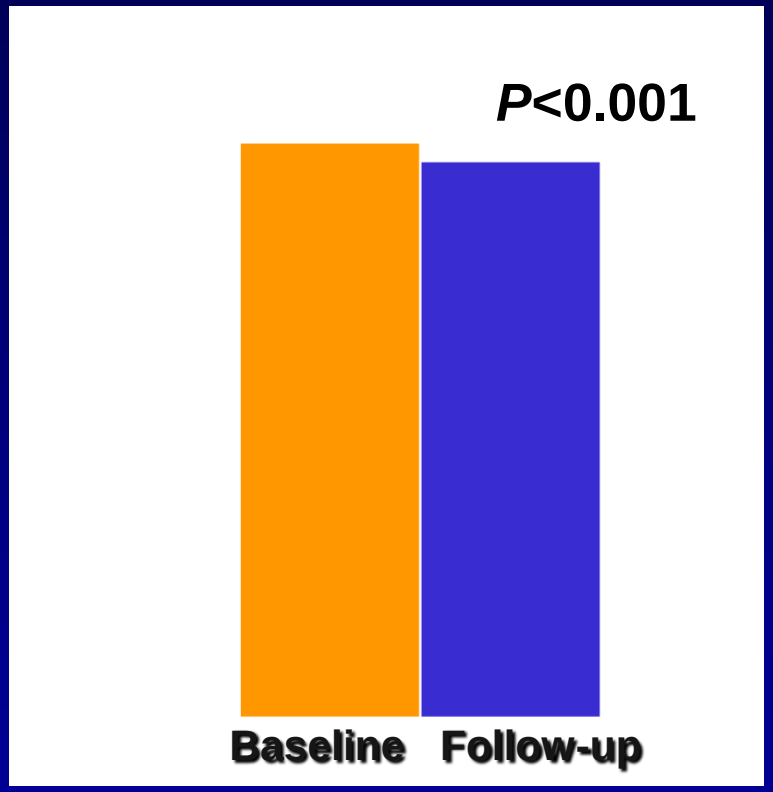
IVUS trials



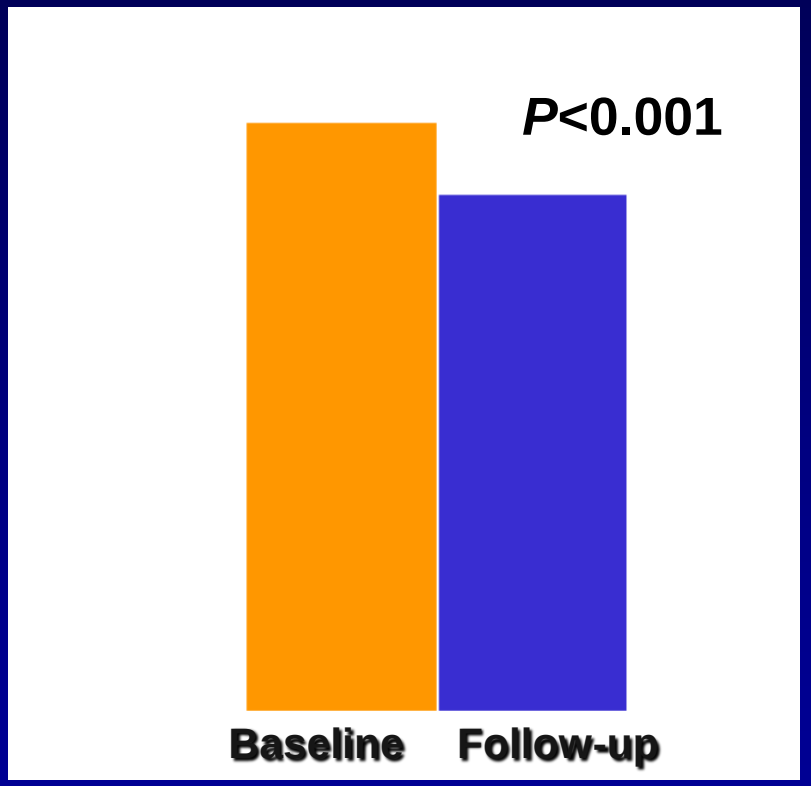
Nissen SE et al. *JAMA*. 2006;295:1556-65.

ASTEROID: IVUS End Points After 24-Month Open-Label Treatment With Rosuvastatin 40 mg

Median % Atheroma Volume



Median Atheroma Volume in Most Diseased Subsegment (mm^2)



	Baseline	Follow-up	% Change
Mean LDL-C	130 mg/dL	61 mg/dL	-53

Nissen et al. *JAMA.* 2006;295:1556-1565.

Towards Medical Therapy of Coronary Disease

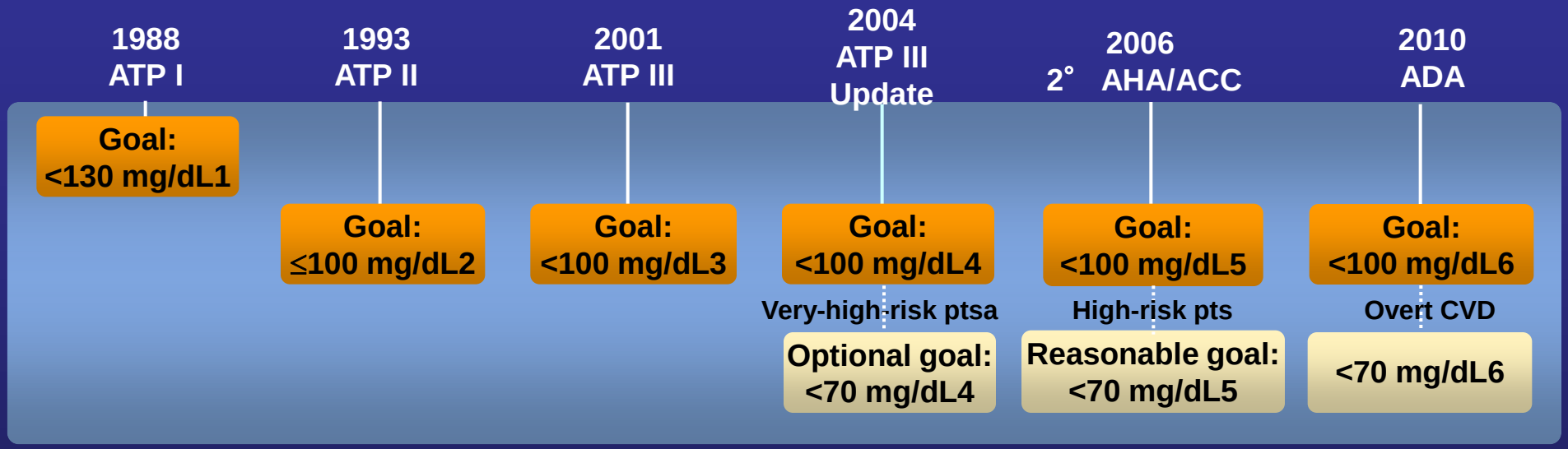
A. Stop Progression (and stabilize the plaque?):

1. Extreme LDL reductions
2. Aggressive RF and T2D management
3. Maybe direct effects of ACE-I/ARB, Statins, ASA

B. Induce Regression (and stabilize the plaque?):

1. Stop progression
2. Maybe activation of HDL pathway
3. Maybe direct effects of PPAR or LXR agonists

Evolution of LDL-C Goals for High-Risk Patients: NCEP Guidelines



Definition of high-risk or highest-risk patient:

- ATP I: definite CHD or 2 other CHD risk factors[1]
- ATP II: prior CHD or other atherosclerotic disease[2]
- ATP III and the 2004 update: CHD or CHD risk equivalents[3,4]
- 2° AHA/ACC 2006: established coronary and other atherosclerotic disease[5]
- ADA 2010: overt CVD[6]

1. NCEP ATP I. *Arch Intern Med*. 1988;148:36–69; **2.** NCEP ATP II. *JAMA*. 1993;269:3015–3023; **3.** NCEP ATP III. *JAMA*. 2001;285:2486–2497; **4.** Grundy SM et al. *Circulation*. 2004;110:227–239; **5.** Smith SC Jr et al. *Circulation*. 2006;113:2363–2372; **6.** ADA. *Diabetes Care*. 2010;33(suppl 1):S11–S61.

A Case

56-yo obese man with T2D, HTN, and HLP
Progressive CHD (4 stents in the last 3 years)
T2D: on Metformin 2000 (HbA1c 6.7%)
HTN: controlled on ACE-I and diuretic
HLP: on atorvastatin 80 mg, fish oil supplement, diet (low sugar, low saturated fats, high fiber, plant sterols, almonds, soy protein, cardboard).
Labs:
LDL 110 mg/dl, TG 210 mg/dl, HDL 39 mg/dl

LDL Hypothesis Under Attack

NCEP Guidelines vs. Tailored Treatment*

Treatment	Age 30-75		Age 65-75	
	Any Dose	High Dose	Any Dose	High Dose
NCEP	**36.8%**	**12.3%**	**66.4%**	**28.4%**
Tailored	**36.6%**	**9.2%**	**91.7%**	**41.1%**

***Simvastatin 40 mg to subjects on the 5-15% CHD risk range, atorvastatin 80 mg for those >15%.**

Hayward RA, Ann Intern Med. 2010;152:69-77

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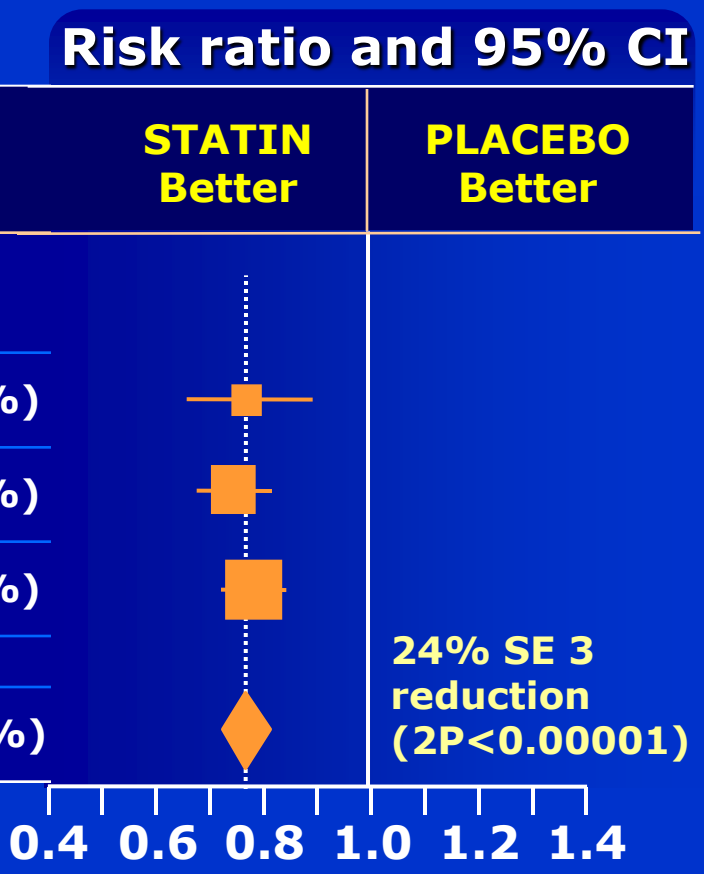
***Simvastatin 40 mg to subjects on the 5-15% CHD risk range, atorvastatin 80 mg for those >15%. Below 5%: NO STATIN FOR YOU!**

Hayward RA, Ann Intern Med. 2010;152:69-77

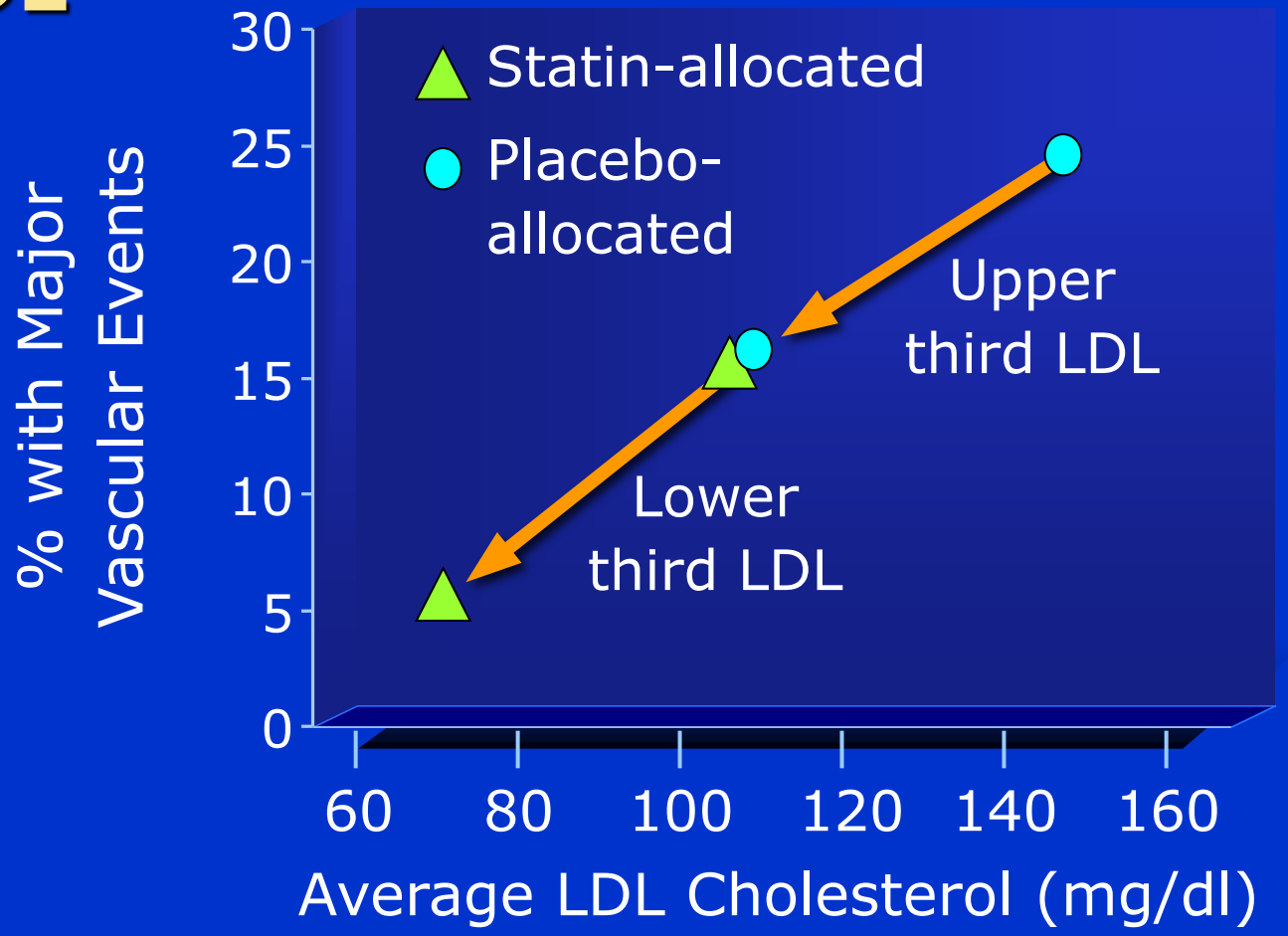
Simvastatin: Major Vascular Events by LDL Cholesterol

Lipid Levels at Entry	Simvastatin (10,269)	Placebo (10,267)
LDL cholesterol (mg/dl)		
< 100	282 (16.4%)	358 (21.0%)
≥ 100 < 130	668 (18.9%)	871 (24.7%)
≥ 130	1083 (21.6%)	1356 (26.9%)
ALL PATIENTS	2033 (19.8%)	2585 (25.2%)



Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.

Simvastatin: Major Vascular Events in Upper and Lower Thirds of Baseline LDL



Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.

The JUPITER Trial

- 18,000 men and women with LDL<130 and hsCRP>2
- No CHD, Diabetes, HTN, or severe dyslipidemia
- 20 mg of rosuvastatin vs placebo
- Stopped early due to a 47% RRR in primary endpoint
- 50% of subjects had LDL<55, and 25% had LDL<44
- Claimed NNT (projected at 5 years) of 25

Ridker, P. NEJM 2008

Benefits of the Tailored Approach

- Goal (ie, use of statin drug) easier to reach
- Cost containment
- Higher risk reduction rates among the elderly

Negatives of the Tailored Approach

- Under-treatment of women and younger subjects
- Under-treatment of FH
- Under-treatment of combined dyslipidemia
- Disincentive to diagnose dyslipidemia
- Disincentive to new drug development

Brief History of Statins

- Developed as a tool to help subjects with FH
- Proven to benefit patients with common HLP
- Proven to benefit subjects without HLP
- Proven to benefit subjects at any level of risk
- Proposed used shortchanges FH subjects

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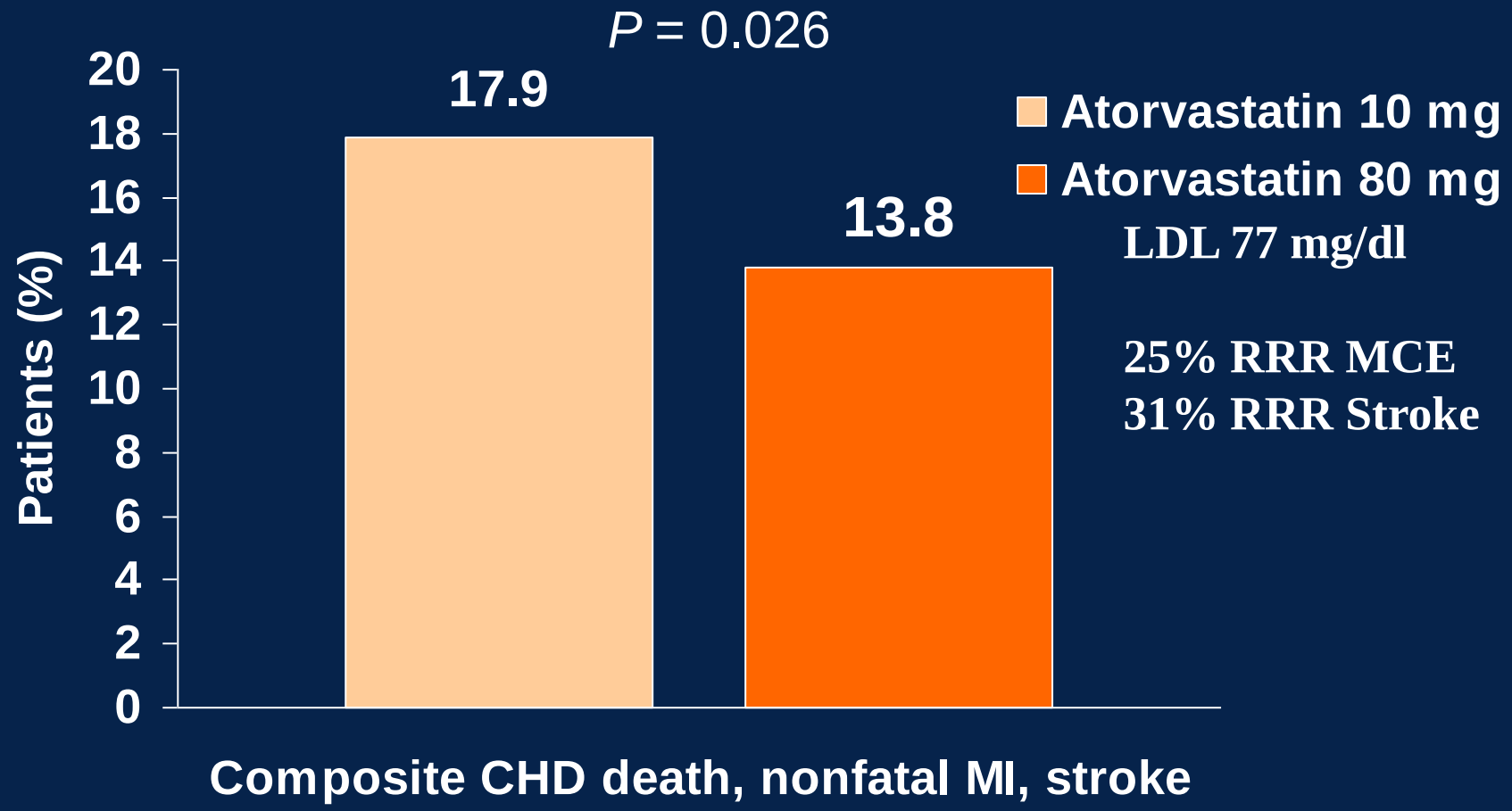
Labs:
LDL 110 mg/dl, TG 210 mg/dl, HDL 39 mg/dl

Does glucose control improve CVD risk in diabetics?

- ADVANCE (6% RRR, ns)
- VADT (no effect)
- ACCORD (10% RRR, ns, CV death up 35%)

NEJM 2008, NEJM 2009

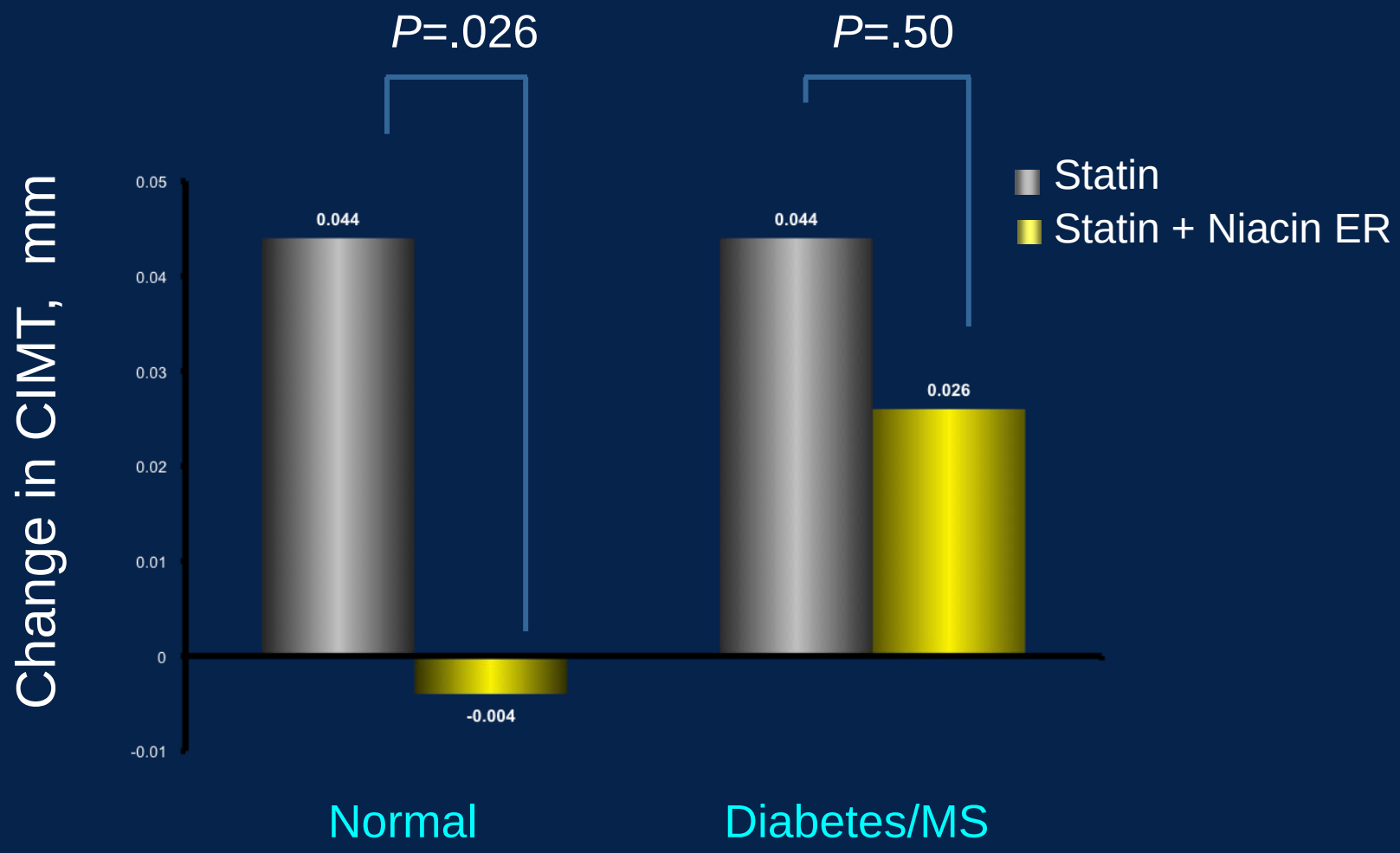
Treating to New Targets (TNT) Results in Patients With Diabetes: Primary Events



MACE = major adverse cardiac event.

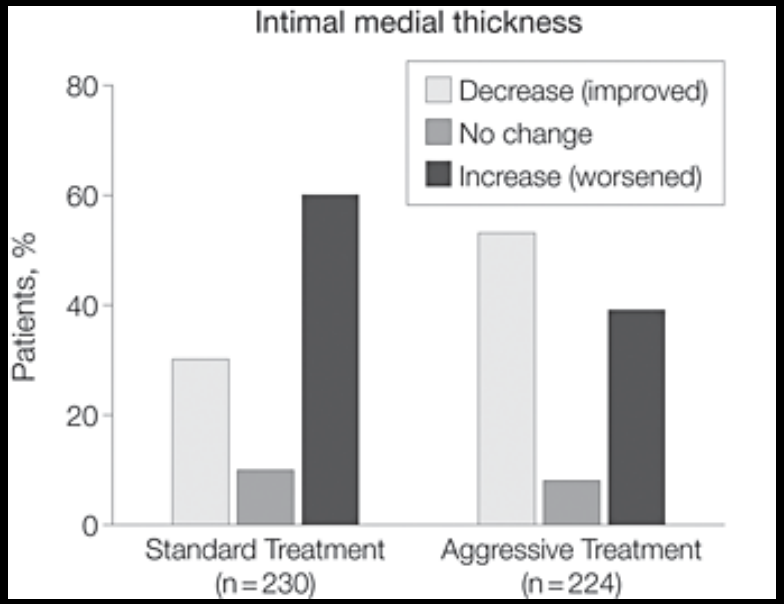
Shepherd J et al. *Diabetes Care.* 2006;29:1220-1226.

ARBITER 2: Patients With and Without Diabetes or Metabolic Syndrome



Taylor AJ, et al. *Circulation*. 2004;110:3512-3517.

SANDS: Categorical Changes in Intimal Medial Thickness by Treatment Group

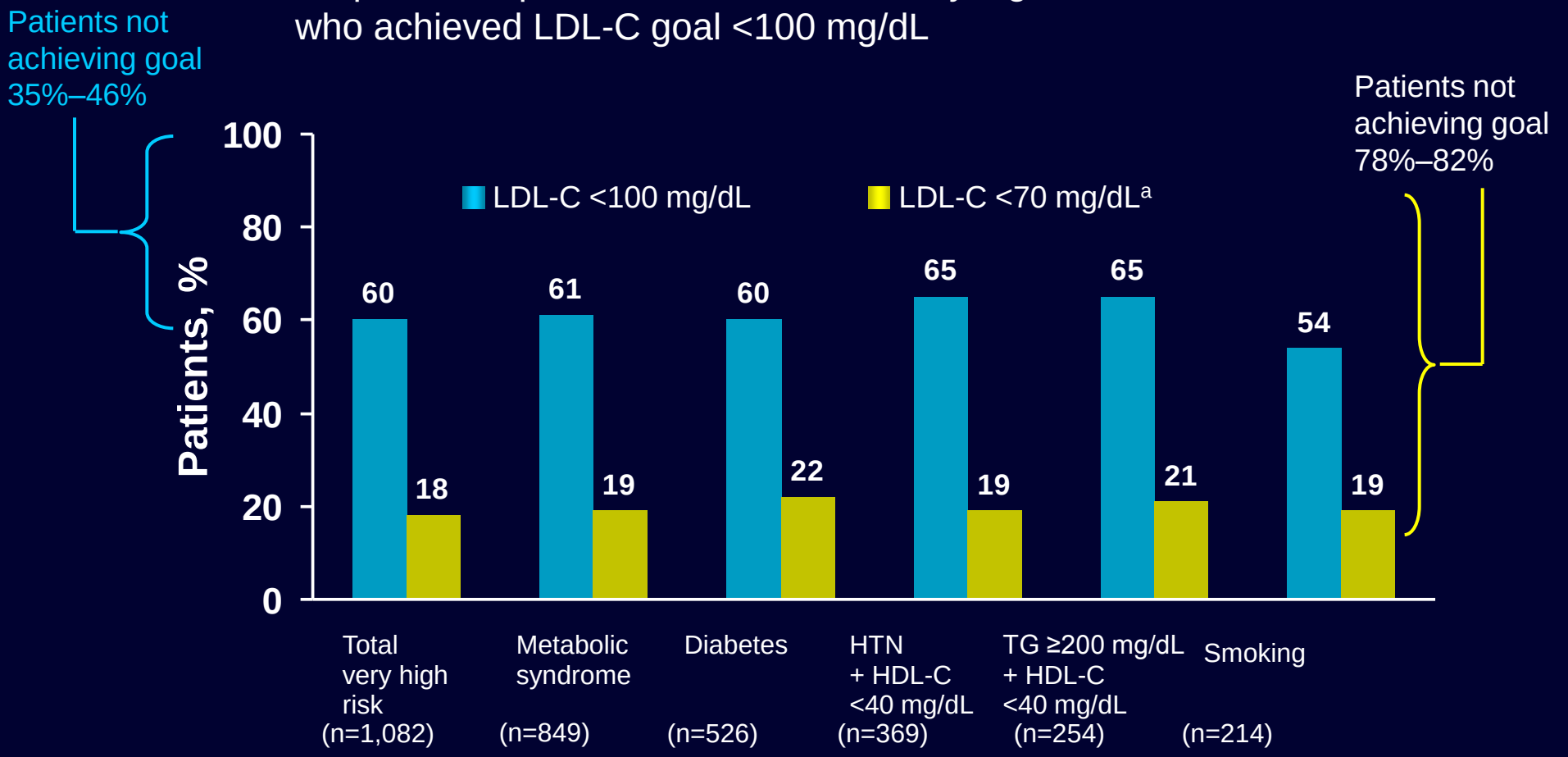


LDL 70 vs 100

Howard, B. V. et al. JAMA 2008;299:1678-1689.

NEPTUNE II: LDL Goals in High-Risk Patients

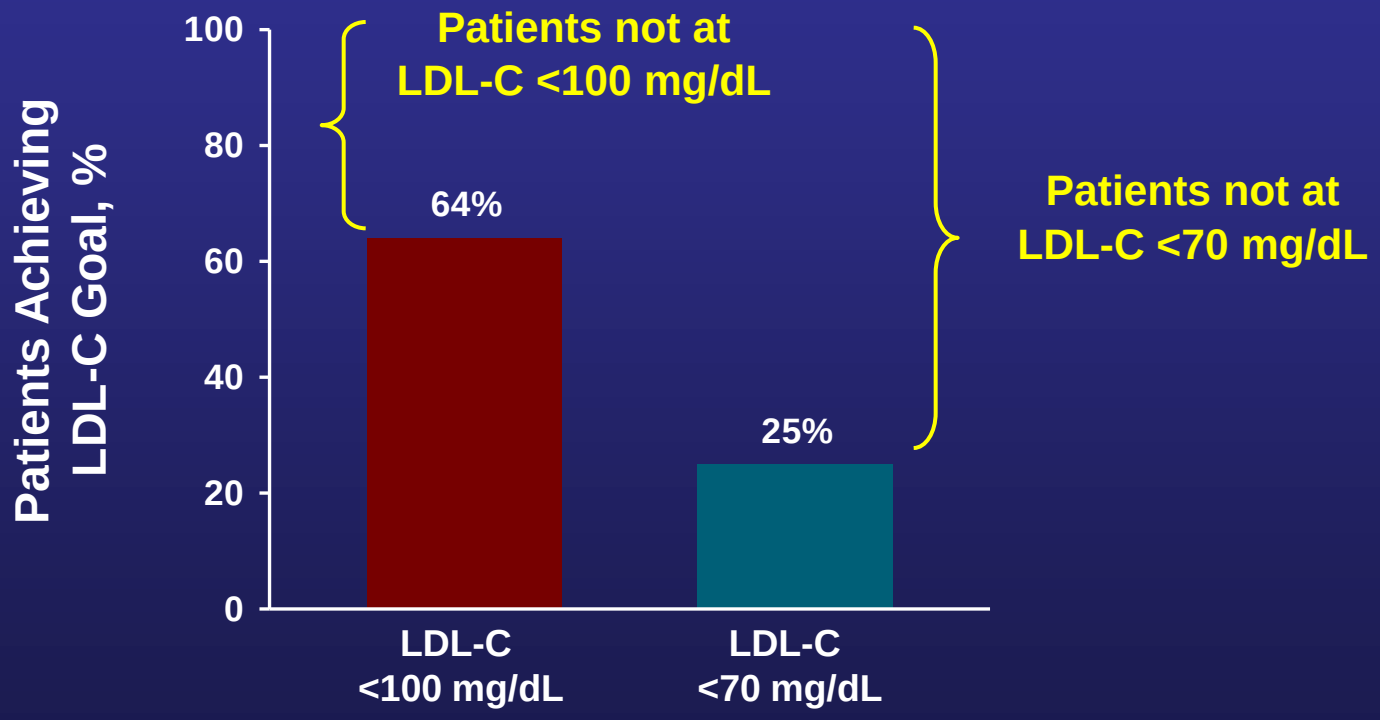
Proportion of patients with CVD and very high-risk characteristics who achieved LDL-C goal <100 mg/dL



NEPTUNE = NCEP Program Evaluation Project Utilizing Novel E-Technology; HTN = hypertension.

Davidson MH et al. *Am J Cardiol*. 2005;96(4):556–563.

Get With The Goal:
Patients on Lipid-Lowering Therapy at Admission[a] for CHD



GWTG = Get With The Guidelines; ACS = acute coronary syndrome; CAD = coronary artery disease.

aPatients on lipid-lowering therapy prior to hospitalization (n=28,944).

1. Sachdeva A et al. *Am Heart J*. 2009;157:111–117.e2.

Triple Therapy Needed by Many

A 64-Week Study on 383 High-Risk Subjects Receiving Ezetimibe/Simvastatin (10/20) +/- ER Niacin (to 2000)

Treatment	LDL<100, apoB<90, non-HDL<130	LDL<70, apoB<80, non-HDL<100
Eze/Simva	58.3%	28.6%
Eze/Simva/ ER Niacin	77.3%	57.1%

Three drugs are not enough to reach the lowest goals.
We need new therapies!

Fazio S, Guyton J, et al. unpublished

Do non-statin drugs improve CVD risk?

- Fibrates (?)
- Ezetimibe (?)
- Niacins (?)
- Omega 3 Fats (✔)

  (but likely not via lipid-lowering)

New LDL Drugs on the Horizon

- ApoB Antisense (mipomersen)
- Selective Thyromimetics (eprotirome)
- PCSK9 Inhibitors
- MTTP Inhibitors

Summary

- LDL lowering is the most effective single CVD risk reduction strategy, with no lower threshold identified
- Statins effectively lower LDL and have produced the bulk of clinical evidence on CVD benefits from lipid modulation.
- An LDL goal of <70 mg/dl is a practical endorsement of widespread use of statin therapy in high-risk subjects; however, combination therapy is needed by many to reach this goal.
- Non-statin drugs must provide proof of benefits to move the field forward and open the way for new, potent, and safe LDL-lowering medications